Remarks

After amendment, claims 1-6 and 13-38 remain pending in the present application. Note that no amendment to the claims have been made to place the application in condition for allowance. It is Applicant's view that the prior does not impact the patentability of the pending claims for the reasons presented hereinbelow and which are supported by the enclosed declaration of the inventor of the present application, Professor Richard Hochberg, Ph.D. We note the Examiner's continued reliance on the prior art of record, but Applicant feels the art is inadequate and fails to teach or suggest the instant invention.

The Examiner continues to assert a single new rejection; that the instant claims are obvious over Van den Broek, US patent no. 3,972,906 ("the '906 patent"). For the reasons which are set forth hereinbelow, it is respectfully submitted that the claims of the instant application are non-obvious over the '906 patent and the application is in condition for allowance. As stated above, the enclosed Declaration of Dr. Richard Hochberg is provided in support of patentability.

The courtesy of the telephonic interview with Examiner Badio on March 13, 2007 is respectfully acknowledged. In that interview, the undersigned attorney presented in greater detail the argument that compounds according to the present invention, as depicted in Figure 2a and b of previously submitted Zhang, et al., *J. Med. Chem.* 48, 1428-1447 (2005) (note the data for E11-1-3 ether and E11-1,4 ether), evidence no activity in the traditional estrogenic assay performed, and agreed to present those arguments in Dr. Hochberg's declaration. That declaration is enclosed.

The §103 Rejection

The Examiner has rejected previously amended claims 1-6 and 13-38 as being unpatentable over the '906 patent. Essentially, it is the Examiner's position that because the '906 patent generically discloses a number of compounds which are said to be potentially useful in the treatment of estrogen-deficiency syndromes, that disclosure suggests the present claims. Applicants respectfully traverse the Examiner's rejection.

Applicant previously enclosed a copy of Jelínková, et al., *Acta Endocrinologica*, 96, 389-393 (1981) ("Jelinkova"), which shows the traditional testing of compounds for estrogenic

activity (uterotropic and/or vaginal activity). This reference clearly supports Applicant's contention that the present compounds were not known from the '906 patent and could not have been known from the '906 patent, because the present compounds are ***inactive*** in the traditional estrogenic assays of Jelinkova which tested uterotopic and/or vaginal activity of compounds thought to have *estrogenic* activity. According to the '906 patent and Jelinkova, in order for a compound to be useful, that compound must test favorably in an assay which tested for uterotropic and/or vaginal) estrogenic activity. However, the present compounds do not evidence activity in the assay of Jelinkova, which was the means of testing for the activity of compounds of the '906 patent.

Thus, the '906 patent cannot possibly motivate the presently claimed compounds, because the presently claimed compounds do not exhibit traditional uterotropic and/or vaginal estrogenic activity which is ***required*** by the '906 patent. This is pointed out in the attached declaration of Professor Richard Hochberg and is further evidenced by the attached paper of Zhang, et al., *J. Med. Chem.*, 48, 1428-1447 (2005) ("the JMedChem article"), which is enclosed. In particular, in the JMedChem article, note especially figure 2a in which a similar compound of Jelinkova, the methoxy methyl analog E2-1,1, is estrogenic but as the11β-sidechain is lengthened to the methoxy ethyl ether (E2-1,2) the compound is *much less estrogenic* and when lengthened again by 1 methylene unit to the methyl propoxy ether it is *inactive* – and instead becomes antiestrogenic- as set forth in figure 2b. The attention of the Examiner is drawn to the fact that the same structure activity holds in an uterotrophic assay (figure 5 of the JMedChem article)- i.e., that as chain length increases at the 11-position, traditional estrogenic activity (as measured by the Jelinkova assay) falls off and its antiestrogenic activity increases. This is completely unexpected. It is also completely contrary to the teachings of the '906 patent. In reality, the '906 patent actually *teaches away* from the present invention.

Thus, the present invention relates to the unexpected properties of the claimed compounds, which are directed to compounds which exhibit estrogenic activity at peripheral sites in a patient's body, such as bone, liver and blood vessels, but which exhibit *anti-estrogenic* activity in other tissues such as the uterus, breast, vagina. The present compounds thus exhibit no uterotropic or vaginal activity, the traditional test of estrogenic activity. They are instead

antiestrogens in those tissues. The present compounds are useful for the treatment of certain secondary conditions or disease states associated with menopause such as osteoporosis, hypercholesterolemia or elevated level of LDL, cardiovascular disease and, in the case of breast tissue, because of the compounds' anti-estrogenic activity, the treatment of breast cancer. The activity of the compounds according to the present invention is novel and unique *vis-à-vis* the disclosure of the '906 patent, which, based upon the assays of Jelinkova, could not have discovered the activity of the instantly claimed compounds. It fact, the '906 patent, read in light of Jelinkova as evidenced by the JMedChem article, *clearly* ***teaches away*** from the present invention. It is respectfully submitted that the present compounds and related methods as claimed are patentable over the '906 patent.

The '906 patent is directed to a large number of steroidal compounds, only a small number of which are even related to the present invention. The broad spectrum of compounds disclosed generically by the '906 patent exhibit *inter alia,* contraceptive, estrogenic, progestational, ovulation-inhibiting, gonad-inhibiting and anabolic properties. Certain compounds of the '906 patent are said to be useful as medicaments in the treatment of estrogen-deficiency-syndromes. As explained above, those of ordinary skill take this to mean that the compounds of the '906 patent exhibit uterotropic and/or vaginal estrogenic activity in assays such as those disclosed by Jelinkova. See the attached Hochberg declaration at paragraphs 15-17.

Contrary to the Examiner's contention, the teachings of the '906 patent do not disclose or suggest the present invention. Compounds according to the present invention are important in that they exhibit mixed anti-estrogenic/estrogenic activity. The estrogenic activity of the present compounds is found at peripheral sites such as bone, liver and blood vessels, but the same compounds exhibit ***anti-estrogenic activity*** in the uterus, breasts, vagina and brain. Thus, the present compounds may be used to treat conditions secondary to menopause *without* the side effects which often occur with estrogen treatment of menopause (breast cancer and endometrial cancer). In fact, the present compounds, instead of causing breast cancer, are actually useful for *treating* (i.e. inhibiting growth) breast cancer. This is activity which is completely unexpected from the teachings of the art. See the attached Hochberg Declaration at paragraphs 19-22.

The present compounds are non-obvious in light of the teachings of the '906 patent. As mentioned, the '906 patent discloses a huge number of steroid compounds having a multitude of

uses and pharmacological effects. While the '906 patent does disclose certain steroidal compounds having general estrogen activity, there is no disclosure of the selective estrogenic/anti-estrogenic activity of compounds according to the present invention. Based upon the disclosure of the '906 patent, the present compounds are non-obvious. Moreover, the attached Jelinkova reference combined with the '906 patent further evidences that the '906 patent clearly ***teaches away*** from the present invention, inasmuch as Jelinkova represents the assay systems in which the '906 patent is to be tested, whereas the present compounds, as exemplified by the JMedChem article, exhibit no estrogenic activity in the Jelinkova-type estrogenic assay and therefore point to the fact that the present invention is non-obvious over the '906 patent. See the attached Hochberg declaration.

The '906 patent discloses that certain compounds possess estrogenic activity. In general, estrogenic activity is assessed in various estrogen responsive models, e.g., estrogen receptor binding, endometrial growth, local vaginal activity and uterotrophic activity. In each of these models, the compounds of the '906 patent disclosure, to the extent they are labeled "estrogenic" would exhibit estrogenic activity, as exemplified by Jelinkova. The present compounds, however, exhibit ***anti-estrogenic activity*** in the assays which are typically used to assess estrogenic activity (see the attached JMedChem article and Hochberg declaration). This is based upon the length of the chain which appears at the C_{11} position (R in the chemical formulation of the claims), which provides selective anti-estrogenic and estrogenic activity. Compounds with shorter chains at the C_{11} position than those presently claimed in the present invention, as evidenced by Jelinkova, exhibit typical broad based estrogenic activity consistent with the teachings of the '906 patent. The presently claimed compounds contain longer chains at the C_{11} position which instill selective anti-estrogenic activity in the uterus, vagina, breasts and brain, but estrogenic activity in bone, liver and blood vessels. See the Hochberg declaration at paragraphs 19-22.

It is respectfully submitted that one of ordinary skill looking to synthesize a series of compounds having estrogenic activity as disclosed by the '906 patent would be "taught away" or "led away" from the present invention inasmuch as the present compounds would be seen to be inactive in any relevant assay testing for estrogenic activity (e.g., Jelinkova). An initial structure activity relationship (SAR) determination would teach one of ordinary skill that compounds of the structure according to the present invention (where the C_{11} position has a longer chain) would exhibit no relevant estrogenic activity for the purposes for which the compounds of the '906

patent were made. Thus, the person of ordinary skill following the teachings of the '906 patent actually would completely fail to recognize that the present compounds should be made inasmuch as the activity/value of the present compounds would be unrecognized from the teachings of the '906 patent. This is confirmed by Jelinkova and the attached JMedChem article.

None of the present compounds would show activity in any of the standard estrogen assays consistent with any useful activity as disclosed by the '906 patent and there is simply no teaching which suggests the compounds of the present invention should be made. Indeed, Jelinkova, in combination with the attached JMedChem article confirms this very point. Rather, the '906 patent motivates away from the present compounds inasmuch as estrogenic activity in the standard assays was viewed as valuable, and the present compounds are essentially inactive in those assays. Thus, it is respectfully submitted that one of ordinary skill would understand from the '906 patent (as confirmed by Jelinkova and the JMedChem article) that the present compounds were of no biological significance, because the present compounds do not exhibit estrogenic activity in the standard assays assessing estrogenic activity consistent with the teachings of the '906 patent. As evidenced by the attached JMedChem article, one of ordinary skill testing the compounds of the '906 patent using the Jelinkova assays would recognize that the longer chain lengths at C_{11} were actually counterproductive to instilling estrogenic activity and that compounds similar to the present invention should not even be made. Consequently, the '906 patent fails to disclose or suggest the presently claimed invention.

It is further noted that each of the claimed pharmaceutical compositions or methods is non-obvious over the disclosure of the '906 patent. The pharmaceutical compositions and methods utilizing the patentable compounds are patentable. Given that there is no teaching of the activity of the presently claimed compounds, and even if one were to synthesize these compounds (an activity taught away, as explained above), one of ordinary skill would find the present compounds to be *inactive* in the traditional estrogen assays. There is thus absolutely no motivation to make a pharmaceutical composition out of any of the compounds of the present invention especially where, as here, the biological activity of the compounds was unrecognizable.

The '906 patent does not disclose or suggest that the present compounds are active in treating osteoporosis, cholesterolemia or elevated LDL levels or cardiovascular disease or that the compounds could be used to treat breast cancer. Moreover, in treating these

conditions/disease states, the present compounds do not exhibit estrogenic activity in the uterus, vaginal area, brain or breast (anti-estrogenic activity) and the failure to exhibit such activity is beneficial to the treatment of the individual conditions or disease states, given that side effects associated with typical general estrogen therapy often result in unfavorable estrogen activity with increased endometrial cancer and breast cancer as side effects. In the present invention, unlike in the use of the prior art compounds, breast cancer is not a side effect, but actually can be treated effectively with the present invention. The present invention, therefore, represents a clear advance in the art because of the advantageous selective anti-estrogenic/estrogenic activity of the presently claimed compounds.

Consequently, it is respectfully submitted that the instantly claimed invention is clearly patentable over the '906 patent. There is no teaching or suggestion in the '906 patent (as confirmed by the attached JMedChem article using the assays of Jelinkova) of the presently claimed compounds or their selective activity in treating conditions secondary to menopause without exhibiting broad-based non-selective estrogenic activity, and there is certainly no motivation to produce such compounds or pharmaceutical compositions given that the compounds initially show no estrogenic activity in assays used to assess estrogenic activity. Finally there is absolutely no suggestion or motivation to use the compounds according to the present invention in the claimed methods, given that the compounds exhibit no estrogenic activity in assays typically used to assess such activity. The present invention is clearly patentable over the '906 patent.

For the above reasons, Applicant respectfully asserts that the claims set forth in the amendment to the application of the present invention are now in compliance with 35 U.S.C. Applicants respectfully submit that the present application is now in condition for allowance and such action is earnestly solicited. Applicants have neither cancelled nor added any claim to the present application.

No fee is due for the presentation of this amendment. A petition for an extension of time is enclosed as is the appropriate fee. If any additional fee is due or any overpayment has been made, please charge/credit Deposit Account No. 04-0838.

May 2, 2007

Respectfully submitted,
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CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service as First Class Mail in an envelope addressed to: "United States Patent and Trademark Office P.O. Box 1450 Alexandria, Virginia 22313-1450" on May 3, 2007.

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